

## REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments, the following remarks, and the attached Rule 1.132 Declaration by Dr. Mascagni.

The claims presently pending in the application are 29-55, inclusive. Claims 29, 41, and 42 have been amended. The amendments are fully supported in the as-filed application. New claims 46-55, inclusive, have been added. These claims are all supported in the as-filed application.

### **1. Amendments to claims**

Independent claim 29 has been amended by deleting the expression "or with a cyclodextrin derivative". Analogous expressions relating to cyclodextrin derivatives have also been deleted from claims 41 and 42. Claims 36 and 37 directed to the specific cyclodextrin derivatives of interest have been cancelled.

Moreover, new claims 45-55 directed to the inclusion complexes between paroxetine and cyclodextrin derivatives which are free of organic solvents, and pharmaceutical compositions containing them have been added. They find complete support in the originally filed claims and specification.

### **2. Declaration**

In the enclosed Declaration an experiment (experiment a) is described, wherein the preparation of Example 5 by Ronsen et al. is repeated replacing the hydroxypropyl- $\beta$ -cyclodextrin by  $\beta$ -cyclodextrin. This cyclodextrin is completely insoluble in ethanol and the experiment demonstrates there is no formation of a complex with paroxetine.

Applicants submit that this evidence supports patentability of the subject-matter of present claim 29, now directed only to inclusion complexes between paroxetine and cyclodextrin.

Again in the enclosed Declaration, the preparation in Example 1 of the original application is reported as experiment b) and the preparation in Example 8 is reported as experiment c), and should serve to establish that the formation of a complex between paroxetine and  $\beta$ -cyclodextrin or hydroxypropyl- $\beta$ -cyclodextrin respectively, does occur according to the present invention.

**3. Re: Claim rejections under 35 U.S.C. § 102**

Claims 29 and 32-44 stand rejected under §102(b) over Ronsen et al. This rejection is respectfully traversed.

Applicants have limited the scope of independent claim 29 to the complexes of paroxetine with non-derivatized cyclodextrins. In view of the foregoing amendment, the Ronsen et al. reference cannot be said to anticipate claim 29. Lack of anticipation is also buttressed in view of experiment a) reported in the Declaration.

In fact, in experiment a), Applicants have proven that it is impossible to prepare complexes of paroxetine with a non-derivatised cyclodextrin by the method disclosed by Ronsen et al. On the contrary, it is evident from experiment b) of the Declaration, that a complex between paroxetine and a non-derivatised cyclodextrin can be obtained in accordance with the present invention.

The Examiner is requested to take note that the newly added independent claim 45, directed to inclusion complexes of paroxetine with a cyclodextrin derivative, includes the

limitations of pending claim 30, namely, that the complexes are in the form of a flowing powder, are free from organic solvents, etc.

New claim 45 is therefore also novel in view of Ronsen et al.

In fact, according to Ronsen et al., Example 5, page 9, an “amorphous paroxetine composition containing hydroxypropyl- $\beta$ -cyclodextrin” is prepared in absolute ethanol. However, nowhere in Ronsen et al. is the formation of a complex between paroxetine and hydroxypropyl- $\beta$ -cyclodextrin, disclosed or even mentioned.

Furthermore, even if Ronsen et al. do not report about the presence or absence of ethanol in the product obtained from Example 5, the presence of ethanol in the final product is confirmed by the Ronsen specification itself. In fact, the starting paroxetine used in Example 5 is the paroxetine prepared as in Examples 1 or 2, that is a paroxetine which still contains, after having been vacuum dried, an amount of ethanol respectively of 4% or of 0.3% by weight (see Ronsen et al., page 7, lines 8-9, and page 8, lines 15-16).

At least the above-referenced amounts of ethanol are, therefore, certainly still present in the final product of the reaction in Example 5, even if a vacuum drying step is carried out after the addition of hydroxypropyl- $\beta$ -cyclodextrin. Even more so, given that in Example 5 further ethanol is added besides that already present in the starting paroxetine, it can safely be presumed that the amount of ethanol in the final product after vacuum drying is even higher than the 4% or 0.3% by weight present in the starting paroxetine.

The product as claimed in newly added claim 45 is, by contrast, an inclusion complex between paroxetine and a cyclodextrin derivative, which is free from any organic solvent, including ethanol, and it is therefore distinguishable from the product disclosed by

Ronsen et al. Since the claims distinguish over the Ronsen reference, the §102(b) rejection has been overcome and should be withdrawn.

Independent claims 29 and 45 are moreover novel in view of Uekama et al.

In fact, Uekama et al. disclose a pharmaceutical composition containing a drug and a peracylated cyclodextrin as a solubilizing agent, adsorbent or clathrating agent (see Uekama et al., col. 2, lines 40-45). Non-derivatized cyclodextrins are not disclosed at all, but only cyclodextrin derivatives consisting of per-C<sub>2-18</sub>-acylated cyclodextrins are disclosed. Moreover, paroxetine is only cited among a plethora of drugs of possible use, and never exemplified. Even less so is the possibility of preparing an inclusion complex between paroxetine and the peracylated cyclodextrin derivatives in the form of a flowing powder free from organic solvents disclosed or even intimated.

Therefore, the subject-matter of claims 29 and 45 was not disclosed in the Uekama et al. reference and accordingly should be considered as novel.

#### **4. Re.: Claim rejections - 35 U.S.C. § 103(a)**

In view of what has been said previously in item 3, applicants consider that the difference between the products disclosed by Ronsen et al. and Uekama et al. on one hand, and the present products as claimed in present claims 29 and 45 on the other hand, should be now completely and manifestly apparent to the Examiner, and the §103(a) rejection for obviousness should be withdrawn.

In fact, none of the cited documents discloses or suggests that an inclusion complex between paroxetine and a non-derivatized cyclodextrin can be formed. Accordingly, claim 29 as amended should be considered unobvious.

As far as the complexes between paroxetine and cyclodextrin derivatives are concerned, none of the cited documents discloses or suggests that such a complex can be obtained in the form of a flowing powder free from organic solvents, so that the newly added claim 45 should also be considered to be unobvious.

Concerning the foregoing, applicants consider that the unobvious difference between the present claim 45 and Ronsen et al. should be evident to the Examiner in view of what has already been acknowledged at page 3 of the Office Action dated 07/24/2003, wherein the Examiner stated that *"Applicant argues convincingly that it is more likely than not that the product in the art does contain some of the organic solvent, ethanol. The reference does not teach or suggest removal of residual ethanol."*

Concerning Uekama et al., besides the previous discussion that paroxetine is not exemplified, and the formation of a complex between paroxetine and a cyclodextrin derivative is not disclosed, the following further explanation is advanced by applicants for the Examiner's consideration.

The compositions of Uekama et al. are intended for trans-mucosal or transdermal administration, and can be in the form of a filmy composition obtained by dissolving the drug and the peracylated cyclodextrin in an organic solvent, or in the form of a powdery or granular composition obtained by dissolving the drug and the peracylated cyclodextrin in an organic solvent (see Uekama et al., col. 7, line 1 and ff.). In particular, ethanol is always used as the solvent for preparing the compositions in the Uekama et al. examples, both the filmy compositions (see col. 8, Examples 3 to 6) and the powdery compositions (see col. 10, Example 13).

This means that the final products obtained in this manner necessarily contain significant amounts of ethanol, and this results in obvious drawbacks from the pharmaceutical point of view.

Besides, this constitutes the technical problem solved by the present invention, but a skilled person faced with the technical problem of preparing a pharmaceutical composition based on paroxetine and free from ethanol, and aware of Uekama et al., would never consider the teachings of Uekama et al. because they teach the preparation of compositions by dissolving the drug and the cyclodextrin derivative in ethanol, which is exactly the opposite of applicants' claimed invention.

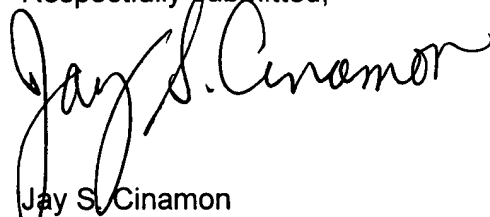
A disincentive to using the teachings of Uekama et al. would also be the fact that they deal with a wholly and completely different technical problem, namely the preparation a pharmaceutical composition for trans-mucosal or trans-dermal administration having a good drug releasability and absorptivity and containing practically any type of drug. The disclosure of Uekama et al. does not deal in any way with the technical problem of having available a pharmaceutical composition for the oral or parenteral administration of paroxetine which is free from ethanol or other organic solvents.

The claims distinguish over the §103(a) rejections and, accordingly, should be withdrawn.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted  
herein to our Deposit Account No. 01-0035.

Respectfully submitted,

A handwritten signature in black ink, reading "Jay S. Cinamon". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

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